In claim 23, please replace "pipecolic acid derivative" with --compound--.

REMARKS

The specification has been amended to correct obvious typographical errors and to describe the inventive subject matter more clearly. Claims 11-20, 22, and 25-26 have been canceled; and claims 1-2, 4-10, and 23 have been amended to describe the inventive subject matter more clearly. Upon entry of the above amendments, claims 1-10, 21, and 23-24 are pending in the application.

The amendments do not introduce new matter within the meaning of 35 U.S.C. §132. Basis for the amendments to Formula VI is found on page 73, line 21 to page 75, line 8. Basis for the amendments to insert references to the uses of the compounds of the invention is found on page 15, lines 3-16 and elsewhere throughout the application. Basis for the claim amendments is found generally on page 34, line 7 to page 44, line 28, particularly page 34, lines 15-18; and elsewhere throughout the specification and claims. Accordingly, entry of the amendments is respectfully requested.

1. Restriction and Election of Species Requirement

In an Office Action dated September 1, 1999, the Examiner required restriction of claims 1-26 under 35 U.S.C. §121 and election of a single species for examination. Applicants provisionally elected Group I and the compound 3-phenylpropyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate as the elected species, with traverse. The Examiner has withdrawn the restriction requirement and imposed a supplemental restriction requirement, requiring restriction to Group I, claims 1-10, 21, and 23-24, drawn to a method of treating vision disorders and memory disorders, or Group II, claims 11-20, 22, and 25-26, drawn to a composition. The Examiner has also required a second species election. To expedite prosecution, Applicants again elect Group I, and have canceled claims 11-20, 22, and 25-26 without prejudice or disclaimer to the subject matter therein. Applicants affirm their prior species election.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the supplemental restriction requirement and supplemental election of species requirement.

2. Objections to the Specification

The Office Action objects to designation of Tables B, C, and D as tables, and requests relabeling as "figure" and refiling in separate sheets. Applicants have amended the Specification as

recommended by the Examiner; Tables B, C, and D are submitted on separate sheets as Figures 10, 11, and 12, and a Brief Description of the Drawings has been added for these Figures.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw these objections.

3. Rejection of Claims 1-5, 10, 21, and 23-24 under Judicially Created Doctrine of Obviousness-type Double Patenting

The Office Action rejects claims 1-5, 10, 21, and 23-24 as being unpatentable under the judicially created doctrine of obviousness-type double patenting over claims 1-7 of U.S. Patent No. 5,798,355 in view of Behl and Bourne.

Applicants respectfully traverse the above rejection. The references of record do not teach or suggest Applicants' inventive subject matter as a whole, as recited in the claims. Further, the art teaches the ordinarily skilled artisan away from the subject matter as defined in the claims.

A. The Office Action Fails to Establish a *Prima Facie* Case.

To establish a *prima facie* case, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir.

1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Finally, the prior art reference(s) must teach or suggest all the limitations of the claims. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

In the present case, a legally sufficient *prima facie* case of obviousness must include a showing of the reasons *why* it would be obvious to use one or more reference compound(s) for the disclosed utility of the present invention.

The '355 patent discloses a method of treating a peripheral neuropathy or treating a neurological disorder related to neurodegeneration. The '355 patent neither teaches nor suggests anything about memory or vision, nor anything about improving vision, treating vision disorders or memory impairment, or enhancing memory performance.

Behl (1997) teaches that "loss of memory is a characterized in neurodegenerative disorder in the Alzheimer's patient".

Bourne, et al. (1998) teaches that "vision impairment and disorders are occurs in association with peripheral neuropathy".

The present application claims methods of "treating a vision disorder, improving vision, treating memory impairment, or

enhancing memory performance". While the Examiner contends that "peripheral neuropathies and neurological disorders relating neurodegeneration (e.g. Alzheimer's disease), are characterized by vision and memory disorders and eventually improve the disease state of vision and memory related diseases", the Examiner does not provide the required factual or technical grounds establishing such inherency; the mere possibility that a certain thing may result from a given set of circumstances is not sufficient.

B. The Claims of the Present Application Are Not Obvious over the Prior Art.

The cited references do not teach or suggest the use of any compound claimed in the present application for treating a vision disorder, improving vision, treating memory impairment, or enhancing memory performance. Under a one-way obviousness determination, an obviousness-type double patenting rejection is improper where the application claims are patentably distinct from the prior patent claims. The claims of the present application are not an obvious variation of the claims of the '355 patent.

The U.S. Supreme Court in *Graham v. John Deere Co.*, 148 U.S.P.Q. 459 (1966) held that non-obviousness was determined under §103 by (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and, (4) inquiring as to any objective evidence of nonobviousness.

In applying the *Graham* test, all of the facts must be considered and it is not realistic within the framework of §103 to pick and chose from certain facts that support a position. Rather, all of the facts of the prior art and the instant invention must be taken into account.

I. The present inventive subject matter

Applicant's claims as presently amended are directed to a method for treating a vision disorder, improving vision, treating memory impairment, or enhancing memory performance in an animal, which comprises administering to said animal an effective amount of a pipecolic acid derivative compound.

II. The prior art

The '355 patent discloses methods of treating a peripheral neuropathy or a neurological disorder related to neurodegeneration. Behl (1997) teaches that "loss of memory is a characterized in neurodegenerative disorder in the Alzheimer's patient". Bourne, et al. (1998) teaches that "vision impairment and disorders are occurs in association with peripheral neuropathy".

III. The differences between the claimed subject matter and the prior art

The Examiner admits that the claims differ because the present invention calls for vision and memory disorders rather than the peripheral neuropathies and neurological disorders related to neurodegeneration disclosed in the '355 patent. The '355 patent

neither teaches nor suggests anything about vision or memory, nor anything about treating a vision disorder, improving vision, treating memory impairment, or enhancing memory performance. The Behl paper merely suggests the use of antioxidant compounds for treating Alzheimer's Disease, but does not teach nor suggest anything about memory impairment or memory performance. The Bourne, et al. paper merely concludes that some unsupported statistical relationship exists between peripheral neuropathies and vision impairment in a limited population of Tanzanian schoolchildren. Bourne, et al. do not teach or suggest anything about treating either peripheral neuropathies or vision impairment, nor anything to suggest that compounds useful for treating peripheral neuropathy are also useful for treating vision disorders or improving vision. There is no teaching in the art that would prompt one of ordinary skill in the art to combine the teachings of the references.

Contrary to the Office Action, the art does not teach that one can predict that compounds useful for treating diverse neurological conditions such as brain trauma, stroke, and the diseases of Alzheimer and Parkinson, would be effective for treating memory impairment. For example, the antidepressant Imipramine is useful in the treatment of Alzheimer's disease, but is not effective in treating the associated memory impairment. Teri, et al., *J. Gerontol.*, 46 (1991) 372-377; copy attached. Similarly, Levodopa

is useful in the treatment of Parkinson's disease, but does not affect the associated memory dysfunction. Owen, et al., *Neuropsychologia*, 35 (1997) 519-532; copy attached.

Similarly, the art does not teach that one can predict that compounds useful for treating peripheral neuropathies would be effective for treating a vision disorder or improving vision. For example, the antidepressant Amitriptyline is useful for treating foot pain associated with peripheral neuropathy; however, Amitriptyline may exacerbate glaucoma. *Physicians Desk Reference*, 53rd Edition, page 3418, middle column; copy attached. Similarly, the anticonvulsant Gabapentin (also known as Neurontin) is useful for treating diabetic peripheral neuropathy. Backonja, et al., *JAMA*, (1998) 280:1831-1836; copy attached. However, Neurontin is marketed with a warning of "frequent" observations of "abnormal vision" during clinical trials. *Physicians Desk Reference*, 53rd Edition, page 2303, right column; copy attached. Further, the antiarrhythmic Mexiletine is also useful for treating diabetic peripheral neuropathy. Wright, et al., *Ann Pharmacother.*, (1997) 31:29-34; copy attached. However, 7.5% of patients in a clinical trial of Mexiletine reported "blurred vision/visual disturbances". *Physicians Desk Reference*, 53rd Edition, page 760, left column; copy attached.

At best, the cited art might make it obvious to try compounds useful for treating neurological disorders related to

neurodegeneration for treating memory disorders, or to try compounds useful for treating peripheral neuropathy for treating vision disorders or improving vision. However, lacking any direction for selecting successful compounds or indication of critical parameters, this is insufficient to support a determination of obviousness.

The method of treating a vision disorder, improving vision, treating memory impairment, or enhancing memory performance of the present invention is unobvious over the prior art.

In view of the above, none of the references, taken singly or in any combination, describe or suggest the methods of the present invention. Applicants therefore submit that the compounds of the present invention are not obvious in view of the cited prior art and there is no basis for reject under the judicially created doctrine of obviousness-type double patenting over U.S. Patent No. 5,798,355.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

CONCLUSION

Based upon the foregoing amendments and remarks, the presently claimed subject matter is enabled and patentably distinguishable over the art of record. The cited art's methods for treating peripheral neuropathy or neurological disorders related to

neurodegeneration do not teach or suggest Applicants' claimed methods of treating a vision disorder, improving vision, treating memory impairment, or enhancing memory performance. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of claims 1-10, 21, and 23-24 and allow all pending claims presented herein for reconsideration. Favorable action with an early allowance of the pending claims is earnestly solicited.

The Examiner is invited to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

NATH & ASSOCIATES PLLC

Date: May 30, 2000

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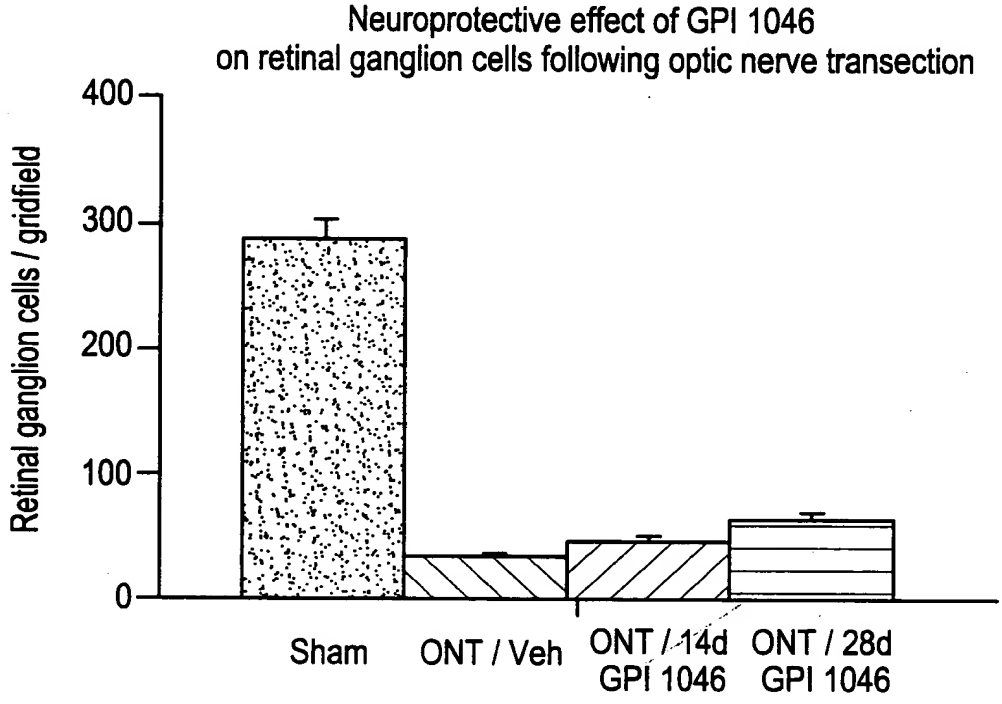
Neuroprotective effect of GPI 1046
on retinal ganglion cells following optic nerve transection
Retinal ganglion cells / gridfield
400
300
200
100
0
Sham
ONT / Veh
ONT / 14d GPI 1046
ONT / 28d GPI 1046

Figure 10

Correlation between Retinal Ganglion Cell and Optic Nerve Axon Sparing at 90 days following optic nerve transection and 14 or 28 day GPI 1046 treatment

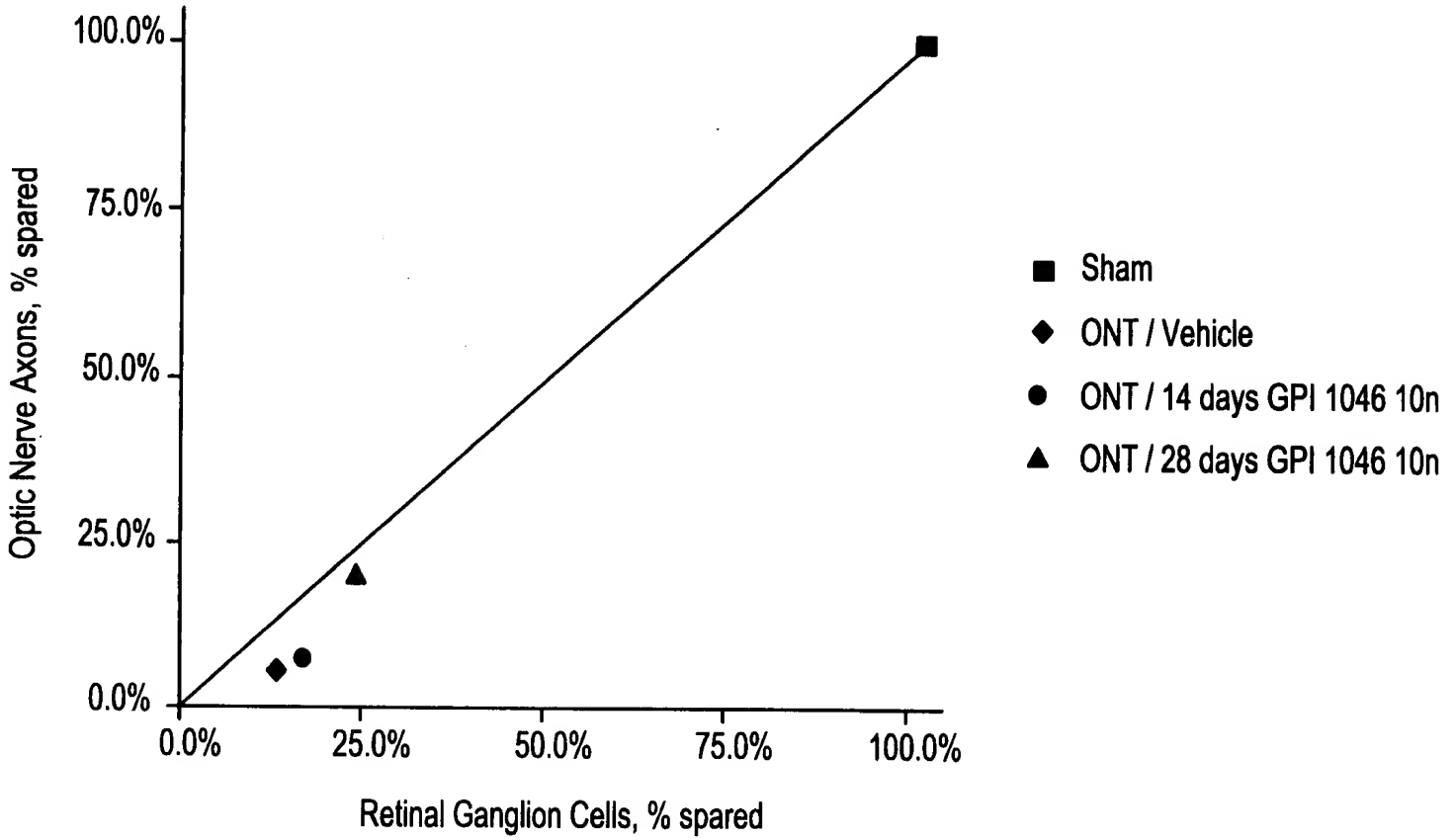

Figure 11